Editorial

Consistently Inconsistent—Bone Marrow Mononuclear Stem Cell Therapy Following Acute Myocardial Infarction
A Decade Later

Timothy D. Henry, Lem Moyé, Jay H. Traverse

A decade ago, 3 potentially groundbreaking trials were published that ushered in a new era of cardiovascular regenerative medicine.1–3 Using autologous bone marrow mononuclear cells (BMCs) in patients with acute ST-segment–elevation myocardial infarction (STEMI), the trials were notable for their clear signal of safety, but discordant in their findings of benefit. Unfortunately, the 1-year results of the SWISS-AMI trial (Swiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction)4 reported in this issue of Circulation Research again remind us about the inability of BMC therapy in patients with STEMI to demonstrate consistent benefit. Why are there such disparate results in trials using a similar cell product in a similar patient population?

The inherent limitations of autologous BMC: The major limitation of autologous BMC may be the considerable patient-to-patient variability related to a decrease in the number and potency of stem cells that occurs with age and cardiovascular risk factors. This was apparent in the...
Delewski meta-analysis3 and well-illustrated in the NIH FOCUS trial (First Mononuclear Cells injected in the United States) using intramyocardial BMC in patients with chronic ischemic heart failure.11 Overall, there was a 2.7% improvement in LVEF in BMC-treated patients. Importantly, patients who were either (1) younger or (2) had a greater number of CD34+ cells had a greater increase in LVEF during the course of the trial, demonstrating the importance of a specific patient’s cell product.

2. The dynamic nature of the condition: After STEMI, there is well-documented upregulation and downregulation of a large number cytokines, growth factors, and inflammatory factors.6 These dynamic cellular changes occur in the setting of improving LVEF over time after successful reperfusion because of resolution of myocardial stunning. Fluctuating changes in both the baseline LVEF measurement and the biological environment make it challenging to detect a cell-based efficacy signal in the presence of this background variability.

3. A not-so-gold standard measure of LV function: Although it is widely thought that MRI is the gold standard for the measurement of LVEF, volumes and infarct size, MRI has many important limitations, including the difficulty distinguishing true infarct from myocardial edema and the significant dropout related to claustrophobia and implantation of defibrillators and pacemakers commonly required in a post-AMI with LV dysfunction patient population. SWISS-AMI nicely illustrates this limitation with the 25% lost to MRI follow-up rate, which was similar to the 15% at 1 year in the TIME trial.15 Also, the considerable changes in technology during the last decade and intercenter variability in technique and analysis make MRI less than a gold standard.

4. The changing natural history of the disease: There has been a dramatic improvement in the clinical outcome of STEMI primarily related to the increased availability of timely reperfusion with PCI and the subsequent growth of regional STEMI systems throughout the world. This is illustrated by the 5.4% 2-year mortality in REPAIR-MI compared with the overall 2-year mortality of 2.3% in SWISS-AMI and <1% at 1 year in TIME, both of which enrolled predominantly high-risk anterior MI patients.4,12 It will be challenging to show a mortality difference with rates <3%, even in selected high-risk patients with LVEF <45%. It is sobering that the 3000-patient BAMI trial (The Effect of Intracoronary Reinfusion of BMC on All Cause Mortality in Acute Myocardial Infarction; NCT01569178) was initially powered for a 12% mortality rate at 2 years.

5. The BMC processing controversy: Although processing of autologous BMC by density centrifugation is theoretically straightforward and inexpensive, there has been a great deal of controversy about the influence of RBCs, the presence of heparin, and processing techniques (Ficoll, Lymphoprep, Sepax).14 These issues exacerbate the small sample sizes and inherent patient variability.

6. The high expectations for the field of cell therapy: The unmitigated (or unbridled) enthusiasm for the potential of cell therapy in the press has created unrealistic expectations in the lay public. This combined with the controversy within the scientific community with those who think that the clinical trials are not warranted, and the proliferation of commercial stem cell centers outside and inside the United States, have provided a challenging if not inimical environment for adequately powered clinical trials.

7. Funding for an adequately powered clinical trial: Absence of a successful business model challenges the provision of sufficient funding for well-powered clinical trials especially with BMC. It is worth remembering that it took 41,021 patients enrolled in the GUSTO trial (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) to show a mortality difference of 6.3% with tissue plasminogen activator versus 7.4% with streptokinase reperfusion.15 It is enlightening to realize the largest trial assessing cell therapy post AMI to date remains the 204-patient REPAIR-AMI trial with the second largest being the 200-patient SWISS-AMI trial 10 years later. Despite the success of the REPAIR-AMI trial and the excitement it generated, the design, initiation, and successful completion of the BAMI trial without the benefit of industry support would be a monumental accomplishment.

8. Accurate identification of high-risk patients: Despite the dramatic improvement in the natural history of STEMI, there are still high-risk patients. Appropriate selection remains the challenge. High-risk patients frequently present with out-of-hospital cardiac arrest or advanced cardiogenic shock and are not well suited for clinical trials. LVEF alone is inadequate (especially early) because of myocardial stunning. The presence of microvascular obstruction seems to identify a high-risk patient population but requires an MRI before enrollment. The index of microcirculatory resistance may be a marker of microvascular obstruction but requires further study.

9. Inadequate potency of BMC: Even in ideal circumstances, unselected BMC may represent a relatively impotent cell product, with limited potential for improving EF or clinical outcomes in patients with AMI. Thus, the discrepant findings likely reflect small treatment effects in relatively underpowered studies. This reality has stimulated many alternative approaches, including allogeneic cells, enhanced or selected autologous cells, and cardiac-derived stem cells.

More than a decade after the initial groundbreaking trials, we are still attracted to the potential and simplicity of BMC for the treatment of patients surviving a large AMI, but now know from experience how difficult this challenge has proven to be. Certainly, considerable knowledge has been gained and we anticipate the results of BAMI, the first adequately powered phase 3 trial but the reality of a cell-based therapy for AMI may be a challenge that remains unmet.

Sources of Funding
This editorial was supported by National Heart, Lung, and Blood Institute Cardiovascular Cell Therapy Research Network grant no. 5 UM1 HL087318.

Disclosures
None.
References


Key Words: Editorials ■ bone marrow ■ myocardial infarction ■ regenerative medicine ■ stem cell
Consistently Inconsistent—Bone Marrow Mononuclear Stem Cell Therapy Following Acute Myocardial Infarction: A Decade Later
Timothy D. Henry, Lem Moyé and Jay H. Traverse

Circ Res. 2016;119:404-406
doi: 10.1161/CIRCRESAHA.116.309231

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/119/3/404

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/